VARIATION DUE TO CHANGE IN THE INDIVIDUAL GENE [1]

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I. THE RELATION BETWEEN THE GENES AND THE CHARACTERS OF THE ORGANISM

THE present paper will be concerned rather with problems, and the possible means of attacking them, than with the details of cases and data. The opening up of these new problems is due to the fundamental contribution which genetics has made to cell physiology within the last decade. This contribution, which has so far scarcely been assimilated by the general physiologists themselves, consists in the demonstration that, besides the ordinary proteins, carbohydrates, lipoids, and extractives, of their several types, there are present within the cell *thousands* of distinct substances—the " genes "; these genes exist as ultramicroscopic particles; their influences nevertheless permeate the entire cell, and they play a fundamental rôle in determining the nature of all cell substances, cell structures, and cell activities. Through these cell effects, in turn, the genes affect the entire organism.

It is not mere guesswork to say that the genes are ultra-microscopic bodies. For the work on *Drosophila* has not only proved that the genes are in the chromosomes, in definite positions, but it has shown that there must be hundreds of such genes within each of the larger chromosomes, although the length of these chromosomes is not over a few microns. If, then, we divide the size of the chromosome by the minimum number of its genes, we find that the latter are particles too small to give a visible image.

The chemical composition of the genes, and the formulæ of their reactions, remain as yet quite unknown. We do know, for example, that in certain cases a given

pair of genes will determine the existence of a particular enzyme (concerned in pigment production), that another pair of genes will determine whether or not a certain agglutinin shall exist in the blood, a third pair will determine whether homogentisic acid is secreted into the urine ('' alkaptonuria ''), and so forth. But it would be absurd, in the third case, to conclude that on this account the gene itself consists of homogentisic acid, or any related substance, and it would be similarly absurd, therefore, to regard cases of the former kind as giving any evidence that the gene *is* an enzyme, or an agglutinin-like body. The reactions whereby the genes produce their ultimate effects are too complex for such inferences. Each of these effects, which we call a '' character '' of the organism, is the product of a highly complex, intricate, and delicately balanced system of reactions, caused by the interaction of countless genes, and every organic structure and activity is therefore liable to become increased, diminished, abolished, or altered in some other way, when the balance of the reaction system is disturbed by an alteration in the nature or the relative quantities of any of the component genes of the system. To return now to these genes themselves.

II. THE PROBLEM OF GENE MUTABILITY

The most distinctive characteristic of each of these ultra-microscopic particles—that characteristic whereby we identify it as a gene—is its property of self-propagation: the fact that, within the complicated environment of the cell protoplasm, it reacts in such a way as to convert some of the common surrounding material into an end-product identical in kind with the original gene itself. This action fulfills the chemist's definition of '' autocatalysis ''; it is what the physiologist would call '' growth ''; and when it passes through more than one generation it becomes '' heredity.'' It may be observed that this reaction is in each instance a rather highly localized one, since the new material is laid down by the side of the original gene.

The fact that the genes have this autocatalytic power is in itself sufficiently striking, for they are undoubtedly complex substances, and it is difficult to understand by what strange coincidence of chemistry a gene can happen to have just that very special series of physico-chemical effects upon its surroundings which produces—of all possible end-products—just this particular one, which is identical with its own complex structure. But the most remarkable feature of the situation is not this oft-noted autocatalytic action in itself—it is the fact that, when the structure of the gene becomes changed, through some " chance variation," the catalytic property of the gene may [2] become correspondingly changed, in such a way as to leave it still *auto*catalytic. In other words, the change in gene structure—accidental though it was—has somehow resulted in a change of exactly *appropriate* nature in the catalytic reactions, so that the new reactions are now accurately adapted to produce more material just like that in the new changed gene itself. It is this paradoxical phenomenon which is implied in the expression " variation due to change in the individual gene," or, as it is often called, " mutation."

What sort of structure must the gene possess to permit it to mutate in this way? Since, through change after change in the gene, this same phenomenon persists, it is evident that it must depend upon some general feature of gene construction—common to all genes—which gives each one a *general* autocatalytic power—a " carte blanche "—to build material of whatever specific sort it itself happens to be composed of. This general principle of gene structure might, on the one hand, mean nothing more than the possession by each gene of some very simple character, such as a particular radicle or " side-chain "—alike in them all—which enables each gene to enter into combination with certain highly organized materials in the outer protoplasm, in such a way as to result in the formation, " by " the protoplasm, of more material like this gene which is in combination with it. In

[2] It is of course conceivable, and even unavoidable, that *some* types of changes do destroy the gene's autocatalytic power, and thus result in its eventual loss.

that case the gene itself would only initiate and guide the direction of the reaction. On the other hand, the extreme alternative to such a conception has been generally assumed, perhaps gratuitously, in nearly all previous theories concerning hereditary units; this postulates that the chief feature of the autocatalytic mechanism resides in the structure of the genes themselves, and that the outer protoplasm does little more than provide the building material. In either case, the question as to what the general principle of gene construction is, that permits this phenomenon of mutable autocatalysis, is the most fundamental question of genetics.

The subject of gene variation is an important one, however, not only on account of the apparent problem that is thus inherent in it, but also because this same peculiar phenomenon that it involves lies at the root of organic evolution, and hence of all the vital phenomena which have resulted from evolution. It is commonly said that evolution rests upon two foundations—inheritance and variation; but there is a subtle and important error here. Inheritance by itself leads to no change, and variation leads to no permanent change, unless the variations themselves are heritable. Thus it is not inheritance *and* variation which bring about evolution, but the inheritance *of* variation, and this in turn is due to the general principle of gene construction which causes the persistence of autocatalysis despite the alteration in structure of the gene itself. Given, now, any material or collection of materials having this one unusual characteristic, and evolution would automatically follow, for this material would, after a time, through the accumulation, competition and selective spreading of the self-propagated variations, come to differ from ordinary inorganic matter in innumerable respects, in addition to the original difference in its mode of catalysis. There would thus result a wide gap between this matter and other matter, which would keep growing wider, with the increasing complexity, diversity and so-called " adaptation " of the selected mutable material.

III. A Possible Attack through Chromosome Behavior

In thus recognizing the nature and the importance of the problem involved in gene mutability have we now entered into a *cul de sac,* or is there some way of proceeding further so as to get at the physical basis of this peculiar property of the gene? The problems of growth, variation and related processes seemed difficult enough to attack even when we thought of them as inherent in the organism as a whole or the cell as a whole—how now can we get at them when they have been driven back, to some extent at least, within the limits of an invisible particle? A gene can not effectively be ground in a mortar, or distilled in a retort, and although the physico-chemical investigation of other biological substances may conceivably help us, by analogy, to understand its structure, there seems at present no method of approach along this line.

There is, however, another possible method of approach available: that is, to study the behavior of the chromosomes, as influenced by their contained genes, in their various physical reactions of segregation, crossing over, division, synapsis, etc. This may at first sight seem very remote from the problem of getting at the structural principle that allows mutability in the gene, but I am inclined to think that such studies of synaptic attraction between chromosomes may be especially enlightening in this connection, because the most remarkable thing we know about genes—besides their mutable autocatalytic power— is the highly specific attraction which like genes (or local products formed by them) show for each other. As in the case of the autocatalytic forces, so here the attractive forces of the gene are somehow exactly adjusted so as to react in relation to more material of the same complicated kind. Moreover, when the gene mutates, the forces become readjusted, so that they may now attract material of the new kind; this shows that the attractive or synaptic property of the gene, as well as its catalytic property, is not primarily dependent on its specific structure, but on some general principle of its make-up, that

causes whatever specific structure it has to be auto-attractive (and autocatalytic).

This auto-attraction is evidently a strong force, exerting an appreciable effect against the non-specific mutual repulsions of the chromosomes, over measurable microscopic distances much larger than in the case of the ordinary forces of so-called cohesion, adhesion and adsorption known to physical science. In this sense, then, the physicist has no parallel for this force. There seems, however, to be no way of escaping the conclusion that in the last analysis it must be of the same nature as these other forces which cause inorganic substances to have specific attractions for each other, according to their chemical composition. These inorganic forces, according to the newer physics, depend upon the arrangement and mode of motion of the electrons constituting the molecules, which set up electro-magnetic fields of force of specific patterns. To find the principle peculiar to the construction of the force-field pattern of genes would accordingly be requisite for solving the problem of their tremendous auto-attraction.

Now, according to Troland (1917), the growth of crystals from a solution is due to an attraction between the solid crystal and the molecules in solution caused by the similarity of their force field patterns, somewhat as similarly shaped magnets might attract each other—north to south poles—and Troland maintains that essentially the same mechanism must operate in the auto-catalysis of the hereditary particles. If he is right, each different portion of the gene structure must—like a crystal—attract to itself from the protoplasm materials of a similar kind, thus moulding next to the original gene another structure with similar parts, identically arranged, which then become bound together to form another gene, a replica of the first. This does not solve the question of what the general principle of gene construction is, which permits it to retain, like a crystal, these properties of auto-attraction,[3] but if the main point is correct, that

[3] It can hardly be true, as Troland intimates, that all similar fields attract each other more than they do dissimilar fields, otherwise all substances would be autocatalytic, and, in fact, no substances would be soluble. More-

the autocatalysis is an expression of specific attractions between portions of the gene and similar protoplasmic building blocks (dependent on their force-field patterns), it is evident that the very same forces which cause the genes to grow should also cause like genes to attract each other, but much more strongly, since here all the individual attractive forces of the different parts of the gene are summated. If the two phenomena are thus really dependent on a common principle in the make-up of the gene, progress made in the study of one of them should help in the solution of the other.

Great opportunities are now open for the study of the nature of the synaptic attraction, especially through the discovery of various races having abnormal numbers of chromosomes. Here we have already the finding by Belling, that where three like chromosomes are present, the close union of any two tends to exclude their close union with the third. This is very suggestive, because the same thing is found in the cases of specific attractions between inorganic particles, that are due to their force field patterns. And through Bridges' finding of triploid *Drosophila*, the attraction phenomena can now be brought down to a definitely genic basis, by the introduction of specific genes—especially those known to influence chromosome behavior—into one of the chromosomes of a triad. The amount of influence of this gene on attraction may then be tested quantitatively, by genetic determination of the frequencies of the various possible types of segregation. By extending such studies to include the effect of various conditions of the environment—such as temperature, electrostatic stresses, etc.—in the presence of the different genetic situations, a considerable field is opened up.

This suggested connection between chromosome behavior and gene structure is as yet, however, only a possibility. It must not be forgotten that at present we can

over, if the parts of a molecule are in any kind of '' solid,'' three dimensional formation, it would seem that those in the middle would scarcely have opportunity to exert the moulding effect above mentioned. It therefore appears that a special manner of construction must be necessary, in order that a complicated structure like a gene may exert such an effect.

not be sure that the synaptic attraction is exerted by the genes themselves rather than by local products of them, and it is also problematical whether the chief part of the mechanism of autocatalysis resides within the genes rather than in the "protoplasm." Meanwhile, the method is worth following up, simply because it is one of our few conceivable modes of approach to an all-important problem.

It may also be recalled in this connection that besides the genes in the chromosomes there is at least one similarly autocatalytic material in the chloroplastids, which likewise may become permanently changed, or else lost, as has been shown by various studies on chlorophyll inheritance. Whether this plastid substance is similar to the genes in the chromosomes we can not say, but of course it can not be seen to show synaptic attraction, and could not be studied by the method suggested above.[4]

IV.   THE ATTACK THROUGH STUDIES OF MUTATION

There is, however, another method of attack, in a sense more direct, and not open to the above criticisms. That is the method of investigating the individual gene, and the structure that permits it to change, through a study of the changes themselves that occur in it, as observed by the test of breeding and development. It was through the investigation of the *changes* in the chromosomes— caused by crossing over—that the structure of the chromosomes was analyzed into their constituent genes in line formation; it was through study of molecular changes that molecules were analyzed into atoms tied together in definite ways, and it has been finally the rather recent finding of changes in atoms and investigation of the resulting pieces, that has led us to the present analysis of atomic structure into positive and negative electrons having characteristic arrangements. Similarly, to understand the properties and possibilities of the individual gene, we must study the mutations as directly as possible, and bring the results to bear upon our problem.

4 It may be that there are still other elements in the cell which have the nature of genes, but as no critical evidence has ever been adduced for their existence, it would be highly hazardous to postulate them.

(a)   *The Quality and Quantity of the Change*

In spite of the fact that the drawing of inferences concerning the gene is very much hindered, in this method, on account of the remoteness of the gene-cause from its character-effect, one salient point stands out already. It is that the change is not always a mere loss of material, because clear-cut reverse mutations have been obtained in corn, *Drosophila, Portulaca,* and probably elsewhere. If the original mutation was a loss, the reverse must be a gain. Secondly, the mutations in many cases seem not to be quantitative at all, since the different allelomorphs formed by mutations of one original gene often fail to form a single linear series. One case, in fact, is known in which the allelomorphs even affect totally different characters: this is the case of the truncate series, in which I have found that different mutant genes at the same locus may cause either a shortening of the wing, an eruption on the thorax, a lethal effect, or any combination of two or three of these characters. In such a case we may be dealing either with changes of different types occurring in the same material or with changes (possibly quantitative changes, similar in type) occurring in different component parts of one gene. Owing to the universal applicability of the latter interpretation, even where allelomorphs do not form a linear series, it can not be categorically denied, in any individual case, that the changes may be merely quantitative changes of some *part* of the gene. If all changes were thus quantitative, even in this limited sense of a loss or gain of part of the gene, our problem of why the changed gene still seems to be autocatalytic would in the main disappear, but such a situation is excluded a priori since in that case the thousands of genes now existing could never have evolved.

Although a given gene may thus change in various ways, it is important to note that there is a strong tendency for any given gene to have its changes of a particular kind, and to mutate in one direction rather than in another. And although mutation certainly does not always consist of loss, it often gives effects that might be termed losses. In the case of the mutant genes for

bent and eyeless in the fourth chromosome of *Drosophila*
it has even been proved, by Bridges, that the effects are
of exactly the same kind, although of lesser intensity, than
those produced by the entire loss of the chromosome in
which they lie, for flies having bent or eyeless in one
chromosome and lacking the homologous chromosome are
even more bent, or more eyeless, than those having a
homologous chromosome that also contains the gene in
question. The fact that mutations are usually recessive
might be taken as pointing in the same direction, since
it has been found in several cases that the loss of genes—
as evidenced by the absence of an entire chromosome of
one pair—tends to be much more nearly recessive than
dominant in its effect.

The effect of mutations in causing a loss in the char-
acters of the organism should, however, be sharply distin-
guished from the question of whether the gene has
undergone any loss. It is generally true that mutations
are much more apt to cause an apparent loss in character
than a gain, but the obvious explanation for that is, not
because the gene tends to lose something, but because
most characters require for proper development a nicely
adjusted train of processes, and so any change in the
genes—no matter whether loss, gain, substitution or rear-
rangement—is more likely to throw the developmental
mechanism out of gear, and give a '' weaker '' result,
than to intensify it. For this reason, too, the most fre-
quent kind of mutation of all is the lethal, which leads
to the loss of the entire organism, but we do not conclude
from this that all the genes had been lost at the time of
the mutation. The explanation for this tendency for most
changes to be degenerative, and also for the fact that
certain other kinds of changes—like that from red to
pink eye in *Drosophila*—are more frequent than others—
such as red to brown or green eye—lies rather in develop-
mental mechanics than in genetics. It is because the
developmental processes are more unstable in one direc-
tion than another, and easier to push '' downhill '' than
up, and so any mutations that occur—no matter what the
gene change is like—are more apt to have these *effects*

than the other *effects*. If now selection is removed in regard to any particular character, these character changes which occur more readily must accumulate, giving apparent orthogenesis, disappearance of unused organs, of unused physiological capabilities, and so forth. As we shall see later, however, the changes are not so frequent or numerous that they could ordinarily push evolution in such a direction against selection and against the immediate interests of the organism.

In regard to the magnitude of the somatic effect produced by the gene variation, the *Drosophila* results show that there the smaller character changes occur oftener than large ones. The reason for this is again probably to be found in developmental mechanics, owing to the fact that there are usually more genes slightly affecting a given character than those playing an essential rôle in its formation. The evidence proves that there are still more genes whose change does not affect the given character at all—no matter what this character may be, unless it is life itself—and this raises the question as to how many mutations are absolutely unnoticed, affecting no character, or no detectable character, to any appreciable extent at all. Certainly there must be many such mutations, judging by the frequency with which "modifying factors" arise, which produce an effect only in the presence of a special genetic complex not ordinarily present.

(b)   *The Localization of the Change*

Certain evidence concerning the causation of mutations has also been obtained by studying the relations of their occurrence to one another. Hitherto it has nearly always been found that only one mutation has occurred at a time, restricted to a single gene in the cell. I must omit from consideration here the two interesting cases of deficiency, found by Bridges and by Mohr, in each of which it seems certain that an entire region of a chromosome, with its whole cargo of genes, changed or was lost, and also a certain peculiar case, not yet cleared up, which has recently been reported by Nilson-Ehle; these important

cases stand alone. Aside from them, there are only two instances in which two (or more) new mutant genes have been proved to have been present in the same gamete. Both of these are cases in *Drosophila*—reported by Muller and Altenburg (1921)—in which a gamete contained two new sex-linked lethals; two cases are not a greater number than was to have been expected from a random distribution of mutations, judging by the frequency with which single mutant lethals were found in the same experiments. Ordinarily, then, the event that causes the mutation is specific, affecting just one particular kind of gene of all the thousands present in the cell. That this specificity is due to a spatial limitation rather than a chemical one is shown by the fact that when the single gene changes the other one, of identical composition, located near by in the homologous chromosome of the same cell, remains unaffected. This has been proved by Emerson in corn, by Blakeslee in *Portulaca,* and I have shown there is strong evidence for it in *Drosophila.* Hence these mutations are not caused by some general pervasive influence, but are due to " accidents " occurring on a molecular scale. When the molecular or atomic motions chance to take a particular form, to which the gene is vulnerable, then the mutation occurs.

It will even be possible to determine whether the entire gene changes at once, or whether the gene consists of several molecules or particles, one of which may change at a time. This point can be settled in organisms having determinate cleavage, by studies of the distribution of the mutant character in somatically mosaic mutants. If there is a group of particles in the gene, then when one particle changes it will be distributed irregularly among the descendant cells, owing to the random orientation of the two halves of the chromosome on the mitotic spindles of succeeding divisions,[5] but if there is only one particle to

[5] This depends on the assumption that if the gene does consist of several particles, the halves of the chromosomes, at each division, receive a random sample of these particles. That is almost a necessary assumption, since a gene formed of particles each one of which was separately partitioned at division would tend not to persist as such, for the occurrence of mutation in one particle after the other would in time differentiate the gene into a number of different genes consisting of one particle each.

change, its mutation must affect all of the cells in a *bloc,* that are descended from the mutant cell.

(c)   *The Conditions under which the Change occurs*

But the method that appears to have most scope and promise is the experimental one of investigating the conditions under which mutations occur. This requires studies of mutation frequency under various methods of handling the organisms. As yet, extremely little has been done along this line. That is because, in the past, a mutation was considered a windfall, and the expression '' mutation frequency '' would have seemed a contradiction in terms. To attempt to study it would have seemed as absurd as to study the conditions affecting the distribution of dollar bills on the sidewalk. You were simply fortunate if you found one. Not even controls, giving the '' normal '' rate of mutation—if indeed there is such a thing—were attempted.[6] Of late, however, we may say that certain very exceptional banking houses have been found, in front of which the dollars fall more frequently— in other words, specially mutable genes have been discovered, that are beginning to yield abundant data at the hands of Nilsson-Ehle, Zeleny, Emerson, Anderson and others. For some of these mutable genes the rate of change is found to be so rapid that at the end of a few decades half of the genes descended from those originally present would have become changed. After these genes have once mutated, however, their previous mutability no longer holds. In addition to this '' banking house method '' there are also methods, employed by Altenburg and myself, for—as it were—automatically sweeping up wide areas of the streets and sifting the collections for the valuables. By these special genetic methods of reaping mutations we have recently shown that the ordinary genes of *Drosophila*—unlike the mutable genes above— would usually require at least a thousand years—prob-

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6 Studies of '' mutation frequency '' had of course been made in the Œnotheras, but as we now know that these were not studies of the rate of gene change but of the frequencies of crossing over and of chromosome aberrations they may be neglected for our present purposes.

ably very much more—before half of them became changed. This puts their stability about on a par with, if not much higher than, that of atoms of radium—to use a fairly familiar analogy. Since, even in these latter experiments, many of the mutations probably occurred within a relatively few rather highly mutable genes, it is likely that most of the genes have a stability far higher than this result suggests.

The above mutation rates are mere first gleanings—we have yet to find how different conditions affect the occurrence of mutations. There had so far been only the negative findings that mutation is not confined to one sex (Muller and Altenburg, 1919; Zeleny, 1921), or to any one stage in the life cycle (Bridges, 1919; Muller, 1920; Zeleny, 1921), Zeleny's finding that bar-mutation is not influenced by recency of origin of the gene (1921), and the as yet inconclusive differences found by Altenburg and myself for mutation rate at different temperatures (1919), until at this year's meeting of the botanists Emerson announced the definite discovery of the influence of a genetic factor in corn upon the mutation rate in its allelomorph, and Anderson the finding of an influence upon mutation in this same gene, caused by developmental conditions—the mutations from white to red of the mutable gene studied occurring far more frequently in the cells of the more mature ear than in those of the younger ear. These two results at least tell us decisively that mutation is not a sacred, inviolable, unapproachable process: it may be altered. These are the first steps; the way now lies open broad for exploration.

It is true that I have left out of account here the reported findings by several investigators, of genetic variations caused by treatments with various toxic substances and with certain other unusual conditions. In most of these cases, however, the claim has not been made that actual gene changes have been caused: the results have usually not been analyzed genetically and were in fact not analyzable genetically; they could just as well be interpreted to be due to abnormalities in the distribution of genes—for instance, chromosome abnormalities like

those which Mavor has recently produced with X-rays—
as to be due to actual gene mutations. But even if they
were due to real genic differences, the possibility has in
most cases by no means been excluded (1) that these genic
differences were present in the stock to begin with, and
merely became sorted out unequally, through random
segregation; or (2) that other, invisible genic differences
were present which, after random sorting out, themselves
caused differences in mutation rate between the different
lines. Certain recent results by Altenburg and myself
suggest that genic differences, affecting mutation rate,
may be not uncommon. To guard against either of these
possibilities it would have been necessary to test the
stocks out by a thorough course of inbreeding beforehand,
or else to have run at least half a dozen different pairs
of parallel lines of the control and treated series, and to
have obtained a definite difference in the same direction
between the two lines of *each* pair; otherwise it can be
proved by the theory of " probable error " that the dif-
ferences observed may have been a mere matter of ran-
dom sampling among genic differences originally present.
Accumulating large numbers of abnormal or inferior
individuals by selective propagation of one or two of the
treated lines—as has been done in some cases—adds noth-
ing to the significance of the results.

At best, however, these genetically unrefined methods
would be quite insensitive to mutations occurring at any-
thing like ordinary frequency, or to such differences in
mutation rate as have already been found in the analytical
experiments on mutation frequency. And it seems quite
possible that larger differences than these will not easily
be hit upon, at least not in the early stages of our investi-
gations, in view of the evidence that mutation is ordi-
narily due to an accident on an ultramicroscopic scale,
rather than directly caused by influences pervading the
organism. For the present, then, it appears most prom-
ising to employ organisms in which the genetic composi-
tion can be controlled and analyzed, and to use genetic
methods that are sensitive enough to disclose mutations
occurring in the control as well as in the treated individ-

uals. In this way relatively slight variations in muta-
tion frequency, caused by the special treatments, can be
determined, and from the conditions found to alter the
mutation rate slightly we might finally work up to those
which affect it most markedly. The only methods now
meeting this requirement are those in which a particular
mutable gene is followed, and those in which many
homozygous or else genetically controlled lines can be
run in parallel, either by parthenogenesis, self-fertiliza-
tion, balanced lethals or other special genetic means, and
later analyzed, through sexual reproduction, segrega-
tion and crossing over.

V.   OTHER POSSIBILITIES

We can not, however, set fixed limits to the possibilities
of research. We should not wish to deny that some new
and unusual method may at any time be found of directly
producing mutations. For example, the phenomena now
being worked out by Guyer may be a case in point. There
is a curious analogy between the reactions of immunity
and the phenomena of ·heredity, in apparently funda-
mental respects,[7] and any results that seem to connect
the two are worth following to the limit.

Finally, there is a phenomenon related to immunity, of
still more striking nature, which must not be neglected by
geneticists. This is the d'Hérelle phenomenon. D'Hérelle
found in 1917 that the presence of dysentery bacilli in
the body caused the production there of a filterable sub-
stance, emitted in the stools, which had a lethal and in
fact dissolving action on the corresponding type of bac-
teria, if a drop of it were applied to a colony of the bac-
teria that were under cultivation. So far, there would
be nothing to distinguish this phenomenon from im-

[7] I refer here to the remarkable specificity with which a particular com-
plex antigen calls forth processes that construct for it an antibody that is
attracted to it and fits it " like lock and key," followed by further proc-
esses that cause more and more of the antibody to be reproduced. *If* the
antigen were a gene, which could be slightly altered by the cell to form the
antibody that neutralized it—as some enzymes can be slightly changed by
heating so that they counteract the previous active enzyme—and if this
antibody-gene then became implanted in the cell so as to keep on growing,
all the phenomena of immunity would be produced.

munity. But he further found that when a drop of the
affected colony was applied to a second living colony, the
second colony would be killed; a drop from the second
would kill a third colony, and so on indefinitely. In
other words, the substance, when applied to colonies of
bacteria, became multiplied or increased, and could be so
increased indefinitely; it was self-propagable. It fulfills,
then, the definition of an autocatalytic substance, and
although it may really be of very different composition
and work by a totally different mechanism from the genes
in the chromosomes, it also fulfills our definition of a
gene.[8] But the resemblance goes further—it has been
found by Gratia that the substance may, through appro-
priate treatments on other bacteria, become changed (so
as to produce a somewhat different effect than before,
and attack different bacteria) and still retain its self-
propagable nature.

That two distinct kinds of substances—the d'Hérelle
substances and the genes—should both possess this most
remarkable property of heritable variation or "muta-
bility," each working by a totally different mechanism,
is quite conceivable, considering the complexity of proto-
plasm, yet it would seem a curious coincidence indeed. It
would open up the possibility of two totally different
kinds of life, working by different mechanisms. On the
other hand, if these d'Hérelle bodies were really genes,
fundamentally like our chromosome genes, they would
give us an utterly new angle from which to attack the
gene problem. They are filterable, to some extent isol-
able, can be handled in test-tubes, and their properties,
as shown by their effects on the bacteria, can then be
studied after treatment. It would be very rash to call
these bodies genes, and yet at present we must confess
that there is no distinction known between the genes and
them. Hence we can not categorically deny that perhaps
we may be able to grind genes in a mortar and cook them
in a beaker after all. Must we geneticists become bac-

8 D'Hérelle himself thought that the substance was a filterable virus para-
sitic on the bacterium, called forth by the host body. It has since been
found that various bacteria each cause the production of D'Hérelle sub-
stances which are to some extent specific for the respective bacteria.

teriologists, physiological chemists and physicists, simultaneously with being zoologists and botanists? Let us hope so.

I have purposely tried to paint things in the rosiest possible colors. Actually, the work on the individual gene, and its mutation, is beset with tremendous difficulty. Such progress in it as has been made has been by minute steps and at the cost of infinite labor. Where results are thus meager, all thinking becomes almost equivalent to speculation. But we can not give up thinking on that account, and thereby give up the intellectual incentive to our work. In fact, a wide, unhampered treatment of all possibilities is, in such cases, all the more imperative, in order that we may direct these labors of ours where they have most chance to count. We must provide eyes for action.

The real trouble comes when speculation masquerades as empirical fact. For those who cry out most loudly against " theories " and " hypotheses "—whether these latter be the chromosome theory, the factorial " hypothesis," the theory of crossing over, or any other—are often the very ones most guilty of stating their results in terms that make illegitimate *implicit* assumptions, which they themselves are scarcely aware of simply because they are opposed to dragging " speculation " into the open. Thus they may be finally led into the worst blunders of all. Let us, then, frankly admit the uncertainty of many of the possibilities we have dealt with, using them as a spur to the real work.

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